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(54) Title: A BIOACTIVE AGENT DELIVERING SYSTEM COMPRISED OF MICROPARTICLES WITHIN A BIODEGRADABLE TO IMPROVE RELEASE PROFILES

(57) Abstract

A composition and method for releasing a bio-active agent or a drug within a biological environment in a controlled manner is disclosed. The composition is a dual phase polymeric agent-delivery composition comprising a continuous biocompatible gel phase, a discontinuous particulate phase comprising defined microparticles and an agent to be delivered. A microparticle containing a bio-active agent is releasably entrained within a biocompatible polymeric gel matrix. The bio-active agent release may be contained in the microparticle phase alone or in both the microparticles and the gel matrix. The release of the agent is prolonged over a period of time, and the delivery may be modulated and/or controlled. In addition, a second agent may be loaded in some of the microparticles and/or the gel matrix.

A BIOACTIVE AGENT DELIVERING SYSTEM COMPRISED OF MICROPARTICLES WITHIN A BIODEGRADABLE TO IMPROVE RELEASE PROFILES

FIELD OF THE INVENTION

The present invention is drawn toward a bioactive agent delivering system that allows for the prolonged and controlled release of a bioactive agent within an *in vitro* or *in vivo* environment. More specifically, the present invention comprises a biodegradable gel matrix and a microparticle system wherein the microparticle is embedded in the biodegradable gel matrix, from which the bioactive agent is released in a controlled manner. The bioactive agents may be located within the microparticle only, or within both the microparticle and the gel matrix.

BACKGROUND OF THE INVENTION

Many biologically active macro-molecules such as peptides/proteins and DNA, effective for gene therapy and a variety of therapeutic applications, have become commercially available through advances in recombinant DNA and other technologies. However, these molecules are limited to parenteral administration due to their susceptibility to degradation in the gastrointestinal tract. Treatment for chronic illnesses or indications may require multiple injections per day over many days, or months. Patient compliance is usually poor. Therefore, it would be highly desirable to develop a system for the delivery of bioactive agents or drugs, in particular, polypeptide or protein drugs, at a controlled rate over a sustained period of time without the above mentioned problems. This system would help to optimize the therapeutic efficacy, minimize the side effects, and thereby improve patient compliance.

Attempts to maintain a steady level of medication using biodegradable polymers have recently attracted considerable attention. These polymers are biodegradable and do not require retrieval after the medication is exhausted. Therefore, they can be fabricated into microspheres, microcapsules or nanospheres with the drug encapsulated in them. Various micro-encapsulation techniques

Yet another object of this invention is to provide a drug delivery system that reduces the "burst" effect associated with microparticle delivery systems, improves the bioavailability and duration of action.

It is a further object of the present invention to provide a dosage form that can suspend the microparticles effectively and prevent plugging of hypodermic needles during administration.

Another object of the present invention is to provide a dosage form that localizes the microparticles in a gel depot that is easy to identify and retrieve, should surgical removal become necessary or prescribed.

It is another object of the present invention to provide a bio-active agent delivery system that localizes and protects the bio-active agent containing microparticles from enzyme degradation.

It is still another object of the present invention to provide a bio-active agent delivery system that enables the practioner to modulate release of the bio-active agent into the biological environment.

A further object of this invention is to provide a drug delivery system for the parenteral administration of hydrophilic and hydrophobic drugs, peptide and protein drugs, hormones, genes, oligonucleotides and anti-cancer agents.

These and other objects may be accomplished through a bio-active agent delivery system that combines two bio-active agent delivery technologies, namely, microparticle delivery and polymeric gel delivery. The agent delivery system of the present invention comprises a gel matrix and a microparticle system wherein the microparticle system is embedded in the gel matrix. One or more agents to be delivered may be located in the microparticle alone or both in the microparticle and the gel matrix. The microparticle-gel delivery system of the present invention can release the agent over a prolonged period of time, at a relatively constant rate. The release profile of the system can be modified by altering the microparticle and/or the gel composition. The gel solution is surface active and slightly more viscous than normal saline. Therefore, it can be a wetting agent and, at the same time, an excellent suspending agent for microparticles. This suspension can be injected smoothly without clogging using a relatively small-gauge needle. After injection, the gel sets and localizes the microparticle suspended in it. The agent

degree. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting as the scope of the present invention will be limited only by the appended claims and equivalents thereof.

As used herein the following terms shall have the assigned meanings:

Singular forms of "a," "an," and "the" include plural referents unless the content clearly dictates otherwise.

"Biocompatible" shall mean any substance that is suitable for uses in an warm-blooded animal or a human body..

"Biodegradable" means that the polymer gel and microparticle can break down or degrade within the body to non-toxic components after or while a bioactive agent has been or is being released.

"Parenteral" shall mean intramuscular, intraperitoneal, intra-abdominal, subcutaneous, and, to the extent feasible, intravenous and intraarterial.

"Bioactive agent", "bio-active agent" or "agent" shall mean any drug, organic compound, substance, nutrient or biologically beneficial agent including proteins, peptides(including polypeptides and oligopeptides), hormones, vaccines, oligonucleotides, nucleic acids, steroids, antibiotics, antibodies, live cells, tissue derived compositions and other pharmaceutically active agents. Suitable drugs are described in such well-known literature references as the Merck Index, the Physicians Desk Reference, and The Pharmacological Basis of Therapeutics. A brief listing of specific agents is provided for illustration purposes only, and shall not be deemed as limiting: anti-cancer agents such as mitomycin, bleomycin, BCNU, carboplatin, doxorubicin, daunorubicin, methotrexate, paclitaxel, taxotere, actinomycin D and camptothecin; antipsychotics such as olanzapine and ziprasidone; antibacterials such as cefoxitin; anthelmintics such as ivermectin; antivirals such as acyclovir; immunosuppressants such as cyclosporin A (cyclic polypeptide-type agent), steroids, and prostaglandins.

"Peptide," "polypeptide," "oligopeptide" and "protein" shall be used interchangeably when referring to peptide or protein drugs and shall not be limited as to any particular molecular weight, peptide sequence or length, field of bioactivity or therapeutic use unless specifically stated.

carprolactone, and the like, to form a new RTG system, or by reacting two or more block copolymers to synthesize the mixed RTG system. The RTG mixtures or blends prepared by the above physical mixing or chemically reacting processes may have the same or different gelation properties and gel qualities.

"Polymer solution," "aqueous solution" and the like, when used in reference to a biodegradable polymer or block copolymer contained in such solution, shall mean a water based solution having a gel forming block copolymer dissolved therein at a functional concentration, and maintained at a temperature above or below the gelation temperature such that gel formation does not occur.

"Biodegradable polyesters" refers to any biodegradable polyester, which is preferably synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, ϵ-caprolactone, ϵ-hydroxy hexanoic acid, γ-butyrolactone, γ-hydroxy butyric acid, δ-valerolactone, δ-hydroxy valeric acid, hydrooxybutyric acids, malic acid, and copolymers thereof.

"Reverse thermal gelation" is the phenomena whereby a solution of a block copolymer spontaneously increases in viscosity, and in many instances transforms into a semisolid gel, as the temperature of the solution is increased above the gelation temperature of the copolymer. For the purposes of the invention, the term "gel" includes both the semisolid gel state and the high viscosity state that exists when geltation conditions are met. When cooled below the gelation temperature, the gel spontaneously reverses to reform the lower viscosity solution. This cycling between the solution and the gel may be repeated because the sol/gel transition does not involve any change in the chemical composition of the polymer system. All interactions to create the gel are physical in nature and do not involve the formation or breaking of covalent bonds.

"Microparticle-agent delivery liquid", "microparticle-agent delivery liquid having reverse thermal gelation properties" or "microparticle-agent delivery liquid having stimuli responsive gelation environment" shall mean a polymer solution that contains a microparticle carrying an agent to be delivered, e.g. a drug (the agent *per se* can either be dissolved or colloidal) suitable for administration to a warm-blooded animal which forms a gelled microparticle/drug depot when the

polyesters such as polylactides, poly(D,L-lactide-co-glycolide)s, polyglcolides, poly(lactic acid)s, poly(glycolic acid)s, poly(D,L-lactic acid-co-glycolic acid)s, poly-ϵ-caprolactone), poly(hydroxybutyric acid), and poly(amino acid)s, polyorthoesters, polyetheresters, polyphosphazines, polyanhydrides, polyesteramides, poly(alkyl cyanoacrylate)s, and blends and copolymers thereof. In a more preferred embodiment, the polymer is a biodegradable polyester or polyester copolymer. In a most preferred embodiment, the polymer is poly(D,L-lactide-co-glycolide) with molecular weight between 5,000 to 70,000 Daltons with a lactide-to-glycolide ratio of 1:1 to 1:0. The polymer end groups can be capped or uncapped with low molecular weight organic radicals.

Many microencapsulation techniques used to incorporate a bio-active agent into a microparticle carrier are taught in the art (USP Nos. 4,652,441, 5,100,669, 4,438,253, and 5,665,428). Commonly employed methods include: (a) phase separation and subsequent organic solvent evaporation (include O/W emulsion, W/O emulsions, O/O' emulsions and W/O/W emulsions), (b) coacervation, (c) melt dispersion; (d) spray drying, (e) spray congealing, (f) air suspension coating; and (h) pan coating.

The use of temperature sensitive biocompatible polymers as the gel matrix is a preferred embodiment of the present invention. For example, a block copolymer having thermal gelation properties wherein the polymer is a gel at physiological temperatures (approx.37 ^{0}C) and is a liquid above or below physiological temperatures would be functional. In the case of a gel having reverse thermal-gelation properties, the block copolymer would be a liquid at temperatures below the gelation temperature and would form a gel at above the gelation temperature. Conversely, a block copolymer having conventional thermal-gelation properties would be a liquid above the gelation temperature and a gel at or below the gelation temperature.

Biocompatible polymers having reverse gelation properties are most preferred for the present invention. For example, when a biocompatible block copolymer having reverse thermal-gelation properties is employed, microparticles containing bioactive agents could be loaded in the block copolymer at below physiological temperatures such as room temperature. Because such block

blocks are relatively hydrophilic B polymer blocks comprising polyethylene glycol (PEG). The A block is preferably a biodegradable polyester synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, ϵ-caprolactone, ϵ-hydroxyhexanoic acid, γ-hydroxybutyric acid, δ-valerolactone, δ-hydroxyvaleric acid, hydroxybutyric acids, malic acid, and copolymers thereof, and the B block is PEG. In the most preferred embodiment, the A block is comprised of poly(D,L-lactide-co-glycolide) and the B block is PEG. Preferably, the triblcok copolymer has an average molecular weight between 300 and 20000 Daltons and contains about 10 to 83% by weight of A block polymer. More preferably, the triblcok copolymer has an average molecular weight between 500 and 5000 Daltons and contains about 51 to 83% by weight of A block polymer.

The polymeric gel is preferably biodegradable and exhibits water solubility at low temperatures and undergoes reversible thermal gelation at physiological mammalian body temperatures. Furthermore, these polymeric gels are biocompatible and capable of releasing the substance entrained within its matrix over time and in a controlled manner. As such, this polymeric gel, or others having desired properties, may be used to control release of various microparticles as described above. These biodegradable polymers are gradually degraded by enzymatic or non-enzymatic hydrolysis in aqueous or physiological environments. The degradation products are polyethylene glycol, lactic acid and glycolic acid. These compounds are relatively innocuous and can easily be excreted or absorbed by the biological system.

A distinct advantage of choosing a RTG system as the polymeric gel matrix in a preferred embodiment of the present invention lies in the ability of the RTG or RTG mixtures to wet and suspend the microparticles. The combination of hydrophobic A-block(s) and hydrophilic B-block(s) renders the block copolymer amphiphilic in nature. In that regard, it functions as a wetting agent. The viscosity of RTG is slightly higher than normal saline, thus it can also be seen as a thickening agent. The combinaiton of these two properties makes RTG an excellent suspending agent for hydrophobic particles.

phase transition may result in the formation of a weak gel. At higher concentrations, a strong gel network is formed.

The polymeric gel may be prepared as disclosed in copending application US application No. 09/396,589 filed on 9/15/99 which are fully incorporated by reference herein. The microparticles carrying a bioactive agent may also be prepared according to methods known in the art. An aqueous solution of drug/microparticle below the gelation temperature forms a drug/microparticle delivery liquid where the drug may be either partially or completely dissolved. When the drug/microparticle is partially dissolved, or when the drug/microparticle is essentially insoluble, the drug-carrying microparticle exists in a colloidal state, such as a suspension or emulsion. This drug/micropartile delivery liquid is then administered parenterally, topically, transdermally, transmucosally, inhaled, or inserted into a cavity such as by ocular, vaginal, transurethral, rectal, nasal, oral, buccal, pulmonary or aural administration to a patient, whereupon it will undergo reversible thermal gelation, or other stimuli responsive gelation.

The main mechanism of *in vivo* degradation of the polymers is by hydrolytic degradation in which enzymes may also play a role. Important factors influencing hydrolytic degradation include water permeability, chemical structure, molecular weight, morphology, glass transition temperature, additives, and other environmental factors such as pH, ionic strength, site of implantation, etc. The duration of sustained delivery can be adjusted from few days up to one year by a person of ordinary skill in the art through proper selection of polymer and fabrication method.

Release of the biologically active agent is usually tri-phasic. It comprises an initial burst or, immediate release of the agent present at or near the surface of the microparticle, a second phase during which the release rate is slow or sometime no bio-active agent is released, and a third phase during which most of the remainder of the biologically active agent is released as erosion proceeds. Any agent, as long as it is suitable for microencapsulation in a microparticle, as is known in the art, can utilize the delivery system described by the current invention.

solution to above the gelation temperature of the polymer prior to administration, or may be caused by raising the concentration of the gel forming polymer to the gel forming concentration, or may caused by additives which cause the gel forming polymer solution to gel, or when any other gelation conditions are met. In either event, the drug carrying microparticle/gel may be administered parenterally, topically, transdermally, transmucosally, inhaled or inserted into a cavity such as by ocular, vaginal, buccal, transurethral, rectal, nasal, oral, pulmonary or aural administration.

This invention is applicable to bio-active agents and drugs of all types including oligonucleotides, hormones, anticancer-agents, and it offers an unusually effective way to deliver polypeptides and proteins. Many labile peptide and protein drugs are amenable to formulation into the microparticle and/or the gel polymer or block copolymers and can benefit from the reverse thermal gelation process described herein. While not specifically limited to the following, examples of pharmaceutically useful polypeptides and proteins may be selected from the group consisting of erythropoietin, oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH antagonists, growth hormone (human, porcine, bovine, etc.), growth hormone releasing factor, insulin, somatostatin, glucagon, interleukin-2 , interferon-α, β, or γ, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), interleukin-11 (IL-11), interleukin-12(IL-12),VEG-F, recombinant hepatitis B surface antigen(rHBsAg), renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins and synthetic analogues, modifications and pharmacologically active fragments thereof, enzymes, cytokines, antibodies and vaccines.

EXAMPLE 1

This example illustrates the agent release profile (*in vitro*) of a microparticle-reverse thermal gelation(RTG) agent delivery system.

Zn-hGH, a representative human growth hormone drug, was incorporated into poly(D,L-lactide-co-glycolide) microspheres using the method described in US Patent 5,100,669, hereby fully incorporated by reference. Approximate 10 mg of the microspheres were weighed in a vial and to the vial was added to 100 μL of RTG solution (20% in 10 mM HEPES buffer, pH 7.0) to suspend the particles. The RTG gel was then set in a 37°C oven and 1 mL of the dissolution medium (100 mM HEPES, pH 7.4 with .02% TWEEN-20, 37°C) was added. The control was the identical microspheres suspended in dissolution medium without RTG. The vials were incubated in a 37°C oven. Buffer was replaced periodically and the amount of hGH released was determined by HPLC. The result is shown in Fig. 1.

The data illustrated in FIG.1 showed that a burst amounting to >80% of the loaded drug was observed when the RTG was absent as compared to <20% from those suspended in the RTG. Therefore, it is evident that the RTG-microparticle system of the present invention effectively reduced the initial burst effect of the microparticle delivery system.

EXAMPLE 2

This example illustrates the agent release profile (*in vivo*) of a microparticle-reverse thermal gelation(RTG) agent delivery system.

Zinc-hGH (12%) poly(D,L-lactide-co-glycolide) microspheres (160 mg) are suspended in 1.5 mL of a RTG(20% in 10 mM HEPES, pH 6.5). Three immuno-suppressed rats each is given 0.3-mL subcutaneous injections of the formulation in the dorsal lateral area. Rats in the control group are given the same dose of the microspheres but the vehicle is normal saline (with 3% low molecular weight carboxymethylcellulose as the suspending agent and 0.5% TWEEN 20). It is noticed that the RTG formulation can be injected smoothly using a 24-gauge needle (due to the excellent wetting and suspending ability of the RTG) while clogging of the needle often occurs in the control. Blood samples are collected periodically and the hGH concentrations in plasma are determined by

and the vehicle is normal saline (with 3% low molecular weight carboxymethylcellulose as the suspending agent and 0.5% TWEEN 20). Injections are smooth using 23-gauge needles. No plugging or clogging is experienced. Blood samples are collected periodically and hGH concentrations in plasma are determined by radioimmunoassay (RIA). Plasma hGH profile of the rats given microparticle-Tetronic® formulation shows a much smaller initial burst of hGH than those obtained from the control group.

EXAMPLE 5

This example illustrates the agent release profile (*in vivo*) of a microparticle-Carbomer 940 agent delivery system. Carbomer is also known as carbopol, or carboxylvinyl polymer.

Similar formulation described in Example 3 is used in this example except that the Pluronic® F127 is substituted with carbomer940(0.5% in 10 mM HEPES, pH 6.0). Rats in the controlled group are given same dose of the microspheres and the vehicle is normal saline (with 3% low molecular weight carboxymethylcellulose as the suspending agent and 0.5% TWEEN 20). Injections are smooth using 23-gauge needles. No plugging or clogging is experienced. Blood samples are collected periodically and hGH concentrations in plasma are determined by radioimmunoassay (RIA). Plasma hGH profile of the rats given microparticle-Carbomer 940 formulation shows a relatively smaller initial burst of hGH than those obtained from the control group.

EXAMPLE 6

This example illustrate the preparation and the agent release profile (*in vivo*) of a non-biodegradable microshperes-RTG drug delivery system.

Ethylcellulose (1.5g) is dissolved in 3 mL of acetonitrile in a container. Zn-hGH (150 mg) is then added to the container and the mixture is emulsified in 75 g of mineral oil containing 2% lecithin. The mixture is stirred (900 RPM) in a hood for >16 hrs using an overhead stirrer. Nitrogen (filtered through a 0.2 μ filter) is swept over the head space of the container to remove solvents. The particles are allowed to settle down and the mineral oil is discarded. Hexane is

from the control group. The elimination rate of these drugs in the microparticle-RTG formulation is significantly smaller than the control.

Three rats of each group are sacrificed 24 hrs after injection. It is found that all microparticles in the test group are trapped in RTG and can be easily identified and removed by a pair of tweezers while the microparticles in the control group are scattered and are very difficult to remove.

EXAMPLE 8

This example illustrate the preparation and the agent release profile (*in vivo*) of a microshperes-RTG drug delivery system wherein the drug is loaded both in the microparticles and the gel matrix.

100 mg Zn-hGH loaded microspheres (10% loading) prepared as described in Example 1 is suspended in 1 mL of RTG solution (20% in 10 mM HEPES buffer, pH 7.0) which contains 1 mg of hGH. Each rat (n=3) is given 300 μL of the microsphere-RTG formulation. Rats in the controlled group are given same dose of the microspheres in normal saline (with 3% low molecular weight carboxymethylcellulose as the suspending agent and 0.5% TWEEN 20) containing same amount of hGH. It is noticed that the RTG formulation can be injected smoothly using a 24-gauge needle (due to the excellent wetting and suspending ability of RTG) while clogging of the needle often occurs in the control. Blood samples are collected periodically and hGH concentration in plasma is determined by radioimmunoassay (RIA). Plasma profile of the rats given RTG formulation shows a lower and broader initial hGH peak than the control group. The elimination rate of the drug in the RTG group is also significantly smaller than the control.

EXAMPLE 9

This example illustrate the preparation and the agent release profile (*in vivo*) of a microparticle-RTG drug delivery system wherein some microparticles contains one drug, some microparticles contains a second drug.

Erythropoietin(Epogen®) is incorporated, at a loading of 10% (w/w), into poly(D,L-lactide-co-glycolide) microspheres using the method described in US

CLAIMS

We claim:

1. A dual phase polymeric agent-delivery composition comprising:

(a) a continuous biocompatible gel phase,

(b) a discontinuous particulate phase comprising defined microparticles; and

(c) an agent to be delivered contained in at least said discontinous particulate phase.

2. The composition according to Claim 1 wherein the bioactive agent is contained in both the continuous biocompatible gel phase and the discontinuous particulate phase.

3. The composition according to Claim 1 wherein the biocompatible gel phase is biodegradable.

4. The composition according to Claim 3 wherein said biodegradable gel comprises a hydrogel.

5. The composition according to Claim 4 wherein said hydrogel is a stimuli responsive gel.

6. The composition according to Claim 5 wherein said stimuli responsive gel is sensitive to stimuli selected from the group consisting of temperature, pH, ionic strength, solvent, pressure, stress, light intensity, electric field, magnetic field and gelating agents.

7. The composition according to Claim 6 wherein said continuous gel phase is formed from block coplymers comprising an effective amount of biodegradable hydrophobic polyester A polymer blocks and polyethylene glycol B polymer blocks.

15. The composition according to Claim 9 wherein the biodegradable hydrophobic polyester comprises between about 20 to 100 mole percent lactide and between about 0 to 80 mole percent glycolide.

16. The composition according to Claim 11 wherein, in the triblock copolymer, each biodegradable block has an average molecular weight of between about 270 and 3000.

17. The composition according to Claim 1 wherein said microparticle is in the form of a member selected from the group consisting of microcapsules, microspheres, and nanospheres.

18. The composition according to Claim 17 wherein said microparticle is in the form of a member selected from the group consisting of microcapsules and microspheres.

19. The composition according to Claim 1 wherein said microparticle is biodegradable.

20. The composition according to Claim 19 wherein said agent is a bioactive agent, a drug, or any agent which can be loaded to the microparticle.

21. The composition according to Claim 20 wherein said drug is a polypeptide or protein, oligonucleotide or gene, hormone, anti-cancer or anti-cell proliferation agent.

22. The composition according to Claim 21 wherein said drug is a polypeptide or protein and is a member selected from the group consisting of oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luliberin, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH antagonists, growth hormone (human, porcine, bovine, etc.), growth hormone releasing factor, insulin, erythropoietin,

27. The composition according to Claim 20 wherein said drug is a member selected from the group consisting of testosterone, estradiol, progesterone, prostaglandins, leuprolide acetate, and synthetic analogues, modifications and pharmaceutically equivalents thereof.

28. The composition according to Claim 20 wherein said drug is an anti-cancer agent selected from the group consisting of mitomycin, bleomycin, BCNU, carboplatin, doxorubicin, daunorubicin, methotrexate, paclitaxel, taxotere, actinomycin D, camptothecin, and synthetic analogues, modifications and pharmaceutically equivalents thereof.

29. The composition according to Claim 1 further comprising a second agent.

30. The composition according to Claim 29 wherein the second agent is a bioactive agent or a drug.

31. The composition according to Claim 30 wherein some microparticles contain the first agent and other microparticles contain the second agent.

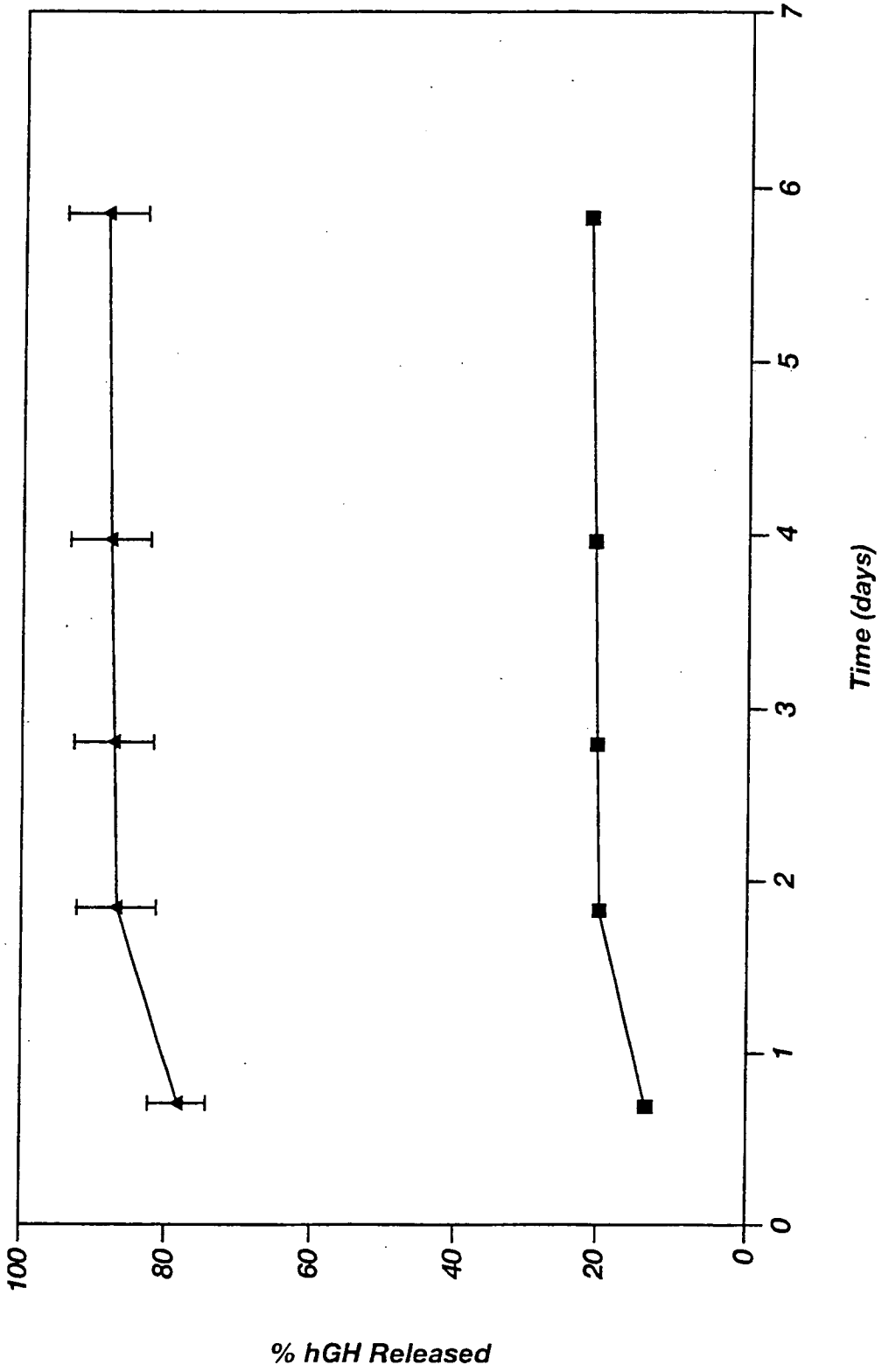
32. The composition according to Claim 30 wherein the gel matrix contains both the first and the second agent.

33. The composition according to Claim 29 wherein the second agent is an agent regulating the release profile of the microparticle.

34. A method for delivering an agent to a biological environment in a controlled manner for a prolonged period of time, comprising the steps of:

(1) providing a dual phase polymeric delivery composition according to Claim 1,

(2) maintaining said composition as a liquid; and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